

## CARCINOMA OF THE STOMACH IN HIROSHIMA, JAPAN \*

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More than 12 years have now passed since the atomic bomb exploded over Hiroshima. Concern about the possible effects of radiation on the well-being of the survivors is frequently expressed. Liebow, Warren and DeCoursey,<sup>1</sup> in their extensive report on atomic bomb casualties, remarked the need for a study of the relationship of radiation to a possible increase in the incidence of neoplasm as one of the major problems to be investigated in Hiroshima and Nagasaki. When the program of the Atomic Bomb Casualty Commission was initiated in 1947, the investigation of this matter was one of its objectives. At that time it was thought possible and, by some, even probable that the delayed effects of radiation would manifest themselves in striking increases in the incidence of a few specific diseases in the exposed populations. A rigid statistical control of the program was not instituted and, indeed, was impossible because of the varying degrees of cooperation offered to the Commission by the survivors. It was recognized that any difference in the incidence of a disease between exposed and nonexposed groups of patients would have to be quite pronounced in order to be detected and to withstand critical evaluation. Significant increase of the incidence of leukemia<sup>2-5</sup> and cataracts<sup>6-8</sup> in the exposed populations have been demonstrated.

In 1955 it was decided that the Pathology Department of the Atomic Bomb Casualty Commission should undertake an investigation of the occurrence of carcinoma of the stomach in both exposed and nonexposed individuals in Hiroshima. The project, as originally outlined, was to determine any differences in incidence, age of onset, or type of gastric tumor occurring in the population group exposed to mass irradiation as compared to a nonexposed population. Carcinoma of the stomach was selected because of its prominent incidence among neoplasms in Japan.

In an extensive survey of the "Geographical Pathology of Cancer in Japan,"<sup>9</sup> Takeda stated that cancer, in general, occurred less frequently in Japan than in Europe and in the United States. If, however, the death rate from carcinoma of the stomach were corrected according to the age distribution of the population, its incidence appeared to be

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higher in Japan than in western countries. Takeda stated that carcinoma of the stomach was the most frequent cancer in both men and women in Japan. He estimated that 43 per cent of all malignant neoplasms in Japanese men occurred in the stomach and that the corresponding figure for women was 30 per cent. The ratio was 1.25 afflicted males to one female in Takeda's series of carcinomas of the stomach; in the United States the ratio is about 1.5. Carcinoma of the stomach is third in frequency among neoplasms occurring in men and fourth in women and accounts for about 35 per cent of all cancer deaths in the United States.<sup>10-15</sup>

#### MATERIALS AND METHODS

The Pathology Department at the Hiroshima Atomic Bomb Casualty Commission initiated full operation in December, 1948. The data listed at present in the diagnostic files have been collected by many Japanese and American pathologists who have been members of the department since that time. From December 1, 1948, through June 30, 1957, members of the department performed 880 necropsies upon adults. Of these, 464 were exposed patients and 416 were nonexposed. During the same period, 11,119 surgical biopsy specimens were examined; 3,185 were procured from exposed patients and 7,915 from nonexposed patients. In 19 cases the locality of the patient on August 6, 1945, could not be determined. In order for an individual to be classified as exposed to the atomic bomb, he must have been within 10,000 meters of the hypocenter when the bomb exploded. This figure was originally selected because one of the borders of Hiroshima City lies at that distance from the hypocenter.

In the necropsy series the principal cause of death was neoplastic disease. Of the 880 patients, 291 or 33 per cent, died as a result of a malignant neoplasm; 153 of these patients had been exposed and 138 had not been exposed to the explosion of the atomic bomb. About 68 per cent of the neoplasms observed in the series were carcinomas, and more than 35 per cent of these were located in the stomach. Carcinoma of the stomach was the most common neoplasm listed in the diagnostic file for both the necropsy and the surgical pathology series.

In undertaking the review of these cases, it was recognized from the outset that the total number of cases might not be large enough to be statistically significant, that the age distribution of the population in Hiroshima was constantly changing and was different for the exposed and nonexposed groups, and that certain other influences might have been introduced into the selection of the patients. The population of Hiroshima has been growing constantly since World War II, and at

present, approximately 90,000 survivors exist in a total population of 400,000. The average age of the survivors is of course somewhat older than that of the nonexposed group because the latter is, to a large extent made up of young newcomers to Hiroshima and children. Both the necropsy and surgical specimens examined at the Atomic Bomb Casualty Commission came from the Hiroshima hospitals. The Commission facilities maintain only 8 beds in internal medicine, and these are used for the study of interesting cases in cooperation with local physicians. No surgical procedures are carried out at the ABCC. Permission to do necropsies is obtained through a departmental necropsy contactor. Two times a day he contacts the City Hall and obtains reports of deaths in Hiroshima. He then approaches the next of kin, either through the attending physician or directly, and asks that the Atomic Bomb Casualty Commission be given permission to perform a necropsy. It is generally not possible to reach all of the families, and occasionally the report of death is delayed beyond the time when the performance of a necropsy would be useful. In the case of a nonexposed individual, if permission for necropsy is at first refused, no further effort is usually made. However, if the patient was among those exposed to the explosion of the bomb or if the attending physician is particularly interested in having a necropsy in either an exposed or nonexposed person, a further effort is made to obtain the consent of the family. Thus, the total number of exposed patients among the 880 necropsied cases was 464, a much higher proportion than would be expected by the ratio of exposed to nonexposed people in the population of Hiroshima. Approximately one fifth of the necropsies, whether on exposed or nonexposed patients, are performed at the direct request of the attending physician. In addition to our Autopsy Service, there are two hospitals in Hiroshima in which necropsies are performed. These hospitals occasionally concede the necropsy examination to the Atomic Bomb Casualty Commission or if the family agrees, invite a member of the department to attend the necropsy and examine the tissues.

The number of surgical pathology specimens examined in Hiroshima is small compared to those in an American city of comparable size. The great majority of specimens are examined at the Atomic Bomb Casualty Commission Pathology Department. Some specimens are received by mail from outlying districts. At the present time, the volume is approximately 2,500 specimens a year, but the number is now rising fairly sharply because of the establishment of a citywide Tumor Registry sponsored jointly by the Hiroshima City Medical Society and the ABCC Department of Pathology. This Registry began function-

ing on May 1, 1957. Our surgical pathology requisition forms and formalin specimen jars are made available and distributed to all of the hospitals and private physicians' offices in Hiroshima. A representative of our Contacting Service visits the different hospitals and other designated collecting points at least 3 times a week in order to pick up new surgical specimens and to return completed reports. No effort is made in the Surgical Pathology Service to emphasize particularly the collection of specimens from exposed patients. However, the information as to exposure is obtained on all patients and made a permanent part of the record. The great majority of the specimens come from gynecologic and general surgical sources. In some instances we have received surgical biopsy specimens from patients who subsequently are necropsied in our department. Thus, the present series of 535 patients with carcinoma of the stomach is represented in our files by a total of 562 surgical and necropsy records because necropsies were performed on 27 patients with carcinoma of the stomach who had been counted previously in the series by reason of surgical specimens. On the basis of reports from the 6 main hospitals and some of the larger private clinics in Hiroshima, it is estimated that about one sixth of the surgical specimens in Hiroshima are received for microscopic examination. Most of the remaining five sixths of the specimens are not examined histologically at the present time.

#### DATA

The 535 patients in this series represent all the cases of carcinoma of the stomach recorded in our surgical or necropsy records from December 1, 1948, through June 30, 1957. All were confirmed by histologic study. There were 342 males and 193 females. This represents a male to female ratio of 1.77 to 1. The male to female ratio in the nonexposed patients was 1.8 to 1, and in the exposed patients 1.7 to 1. Of the total number of specimens, 461 were first examined as surgical specimens and 74 were first encountered at necropsy. In the Autopsy Service, a total of 101 carcinomas of the stomach were observed, but 27 of these had been included in the series by reason of earlier surgical specimens. Of the 461 specimens first seen in the Surgical Pathology Service, 132 were procured from exposed patients. Of the 74 cases in the necropsy group, 55 were exposed patients. Of the males, 224 were nonexposed control cases and 118 were exposed. Of the females, 124 were nonexposed and 69 were exposed.

The males in the series ranged in age from 22 years to 85 years, with an average age of 55.7 years. The females ranged from 23 years to 81 years, with an average age of 51 years. The average age of the non-

exposed males was 53.6 years and the nonexposed females, 48.4 years. The average age of the exposed males was 59.4 years and the exposed females, 52 years.

In 438 cases the description of the neoplasm was sufficiently complete to establish its location in the stomach. In the other cases either the description was incomplete or only a small fragment of the specimen was sent in by the surgeon with only the statement "tumor of the stomach." In two cases there were two separate carcinomas of the stomach. One was obtained from an exposed patient and had separate carcinomas on the posterior wall and on the greater curvature. The second was not exposed and had separate carcinomas in the pylorus and in the cardia. The distribution of the lesions according to the descriptions is indicated in Table I. The regions cited represent the apparent main location of the lesion. Most of the tumors along the lesser curvature also extended to either the anterior or posterior wall or both, and about 80 per cent of them extended into the prepyloric region.

TABLE I  
*Distribution of Gastric Carcinomas*

Pylorus	66
Prepyloric region (including antrum)	107
Lesser curvature	185
Greater curvature	33
Limited to anterior wall	15
Limited to posterior wall	22
Fundus (anterior or posterior wall or curvature not specified)	6
Diffuse ( <i>limitis plastica</i> )	4
Total	438

TABLE II  
*Histologic Pattern of Gastric Carcinomas*

Adenocarcinoma	304
Mucinous adenocarcinoma	95
Undifferentiated carcinoma	102
Papillary adenocarcinoma	20
<i>Limitis plastica</i> —undifferentiated	9
Adenocanthoma	2
Unknown	3
Total	535

The histologic patterns were noted and the sections were reviewed (Table II). Although it was recognized that carcinomas of the stomach are all derived from glandular epithelium, it was possible to separate them into several histologic types. A previously published Japanese report<sup>16</sup> indicated that histologic differences between carcinomas of the stomach in exposed and nonexposed patients could be detected. We were unable to confirm this observation.

An attempt was made to establish the date of death or survival to the end of 1956 in all the patients from whom the 405 surgical specimens were procured. This inquiry was made through the local physician or hospital or by letter to the last known address of the family.

In 153 cases the follow-up was unsuccessful. In 159 cases the date of death was established, and in 93 instances the patient was found to be still alive in February, 1957. Of the 93 living patients, 28 had been exposed to the atomic bomb and 65 had not. The duration of survival is shown in Table III.

TABLE III  
*Duration of Survival, Living Patients*

Duration of survival	Number of patients
More than 6 years	2
5 to 6 years	5
4 to 5 years	1
3 to 4 years	12
2 to 3 years	16
1 to 2 years	22
One year or less	35
Total	93

TABLE IV  
*Distance from Hypocenter, Patients with Gastric Carcinoma*

Distance	Number of patients
Less than 1,000 M.	2
1,000 to 1,500 M.	31
1,500 to 2,000 M.	30
2,000 to 2,500 M.	38
2,500 to 10,000 M.	86
Total	187

All of the patients, of course, had had surgical treatment for the neoplasm. The usual therapy for carcinoma of the stomach as carried out in Japan is a subtotal resection of the stomach with a partial or total resection of the omentum and regional lymph nodes. Total gastrectomy is usually not done. As can be seen in Table III, the very low 5 year survival prevailing in western countries is also found in Japan.

In the patients who were operated on and who subsequently died, the postoperative survival time was investigated to determine if there was any significant difference between the exposed and control groups. In all of the necropsy cases and in 159 of the surgical cases, the date of death was known. In only 20 of the 74 necropsy cases had gastrectomy been performed. It was possible to calculate the postoperative survival time in 179 patients who had died. Of this total, survival ranged from 0 to 51 months with an average of 9.2 months. The number of patients in the exposed group was 99, and their average survival time was 9.2 months. The average survival time for 80 nonexposed patients was 9.16 months. It will be noted that there was no difference in the average survival time between the control and exposed patients.

Of the 187 exposed patients in this series, there was a history of acute radiation illness in 16 cases. In 81 cases there was a definite denial of acute radiation sickness, and in 90 cases a radiation illness history was not taken. A complete history of acute radiation illness was available only in those patients who had attended the ABCC Out-

patient Department during life or had been necropsied. In the patients from whom only surgical biopsy specimens were received, the complete questionnaire concerning acute radiation illness was usually not available. The criteria for establishing the existence of acute radiation illness was based upon a history of epilation, oropharyngeal lesions, bleeding gums and purpura, any or all of which must have occurred within the first 60 days after the explosion of the atomic bomb on August 6, 1945. The farthest distance from the hypocenter for any of the 16 patients was 2,300 meters. It has been noted that the majority of patients who had signs and symptoms of acute radiation illness were within 2,000 meters of the hypocenter at the time of exposure,<sup>3,17</sup> and among the 16 patients only 3 were located at a greater distance when the bomb exploded. Only 2 of the patients in the carcinoma of the stomach series were exposed at less than 1,000 meters. The closest was at a distance of 600 meters, and this patient had had definite signs and symptoms of acute radiation illness, including oropharyngeal lesions, bleeding gums, purpura and epilation. He was 34 years old at the time of the bombing. The other patient was exposed at 780 meters, and he had not had acute radiation illness. The second patient was 60 years old in 1945. It is apparently impossible to determine which of the patients exposed at 2,000 meters or less had had acute radiation illness. In spite of the fact that only 16 of the patients had had radiation illness, 101 patients had been exposed at distances under 2,500 meters (Table IV).

Of course, the importance given to the distance of an exposed individual from the hypocenter must be qualified by the amount of radiation actually received. This was affected by shielding and perhaps by individual biologic variation. LeRoy<sup>18</sup> and others<sup>19</sup> have pointed out that bone marrow depression, as evidenced by leukopenia, occurred even in the absence of other symptoms of the acute radiation syndrome. Thus, individuals may have suffered radiation illness without overt manifestations. In addition, many errors of exaggeration and omission may have entered into the histories, especially since they were obtained as long as 12 years after the event. However, the fact remains that there are wide variations in the effects of acute radiation as indicated by histories from patients exposed at distances of 2,500 meters or less.

The incidence of carcinoma of the stomach among the exposed and the nonexposed patients listed in the combined necropsy and surgical records was calculated. This was also done for all neoplasms found in these groups. The results, as seen in Tables V and VI, show that there was no significant variation between the exposed and nonexposed groups, either for the incidence of carcinoma of the stomach or for

that of all neoplasms. In making these calculations, 18 cases were subtracted from the total number of patients necropsied in the exposed group and 9 from the control group because these cases had already been entered in the series in the surgical pathology group.

On the chance that the patients exposed between 2,500 meters and 10,000 meters had received so little radiation that for the purposes of

TABLE V  
*Incidence of Carcinoma of the Stomach in the Necropsy and Surgical Pathology Files, Compared with Distance From the Hypocenter*

	Total patients exposed under 10,000 meters	Total patients not exposed	Total patients exposed under 2,500 meters	Patients exposed from 2,501 to 10,000 meters & all nonexposed patients
All necropsy cases, Hiroshima ABCC	464	416	306	574
All surgical pathology cases, Hiroshima ABCC	3,185	7,915	1,780	9,320
Total specimens	3,649 (3,631 patients)	8,331 (8,322 patients)	2,086 (2,074 patients)	9,894 (9,879 patients)
Patients with carcinoma of the stomach	187	348	101	434
Percentage, carcinoma of the stomach, necropsy and surgical cases	5.2%	4.2%	4.9%	4.4%

TABLE VI  
*Incidence of All Malignant Neoplasms in the Necropsy and Surgical Pathology Files, Compared with Distance From the Hypocenter*

	In patients exposed under 10,000 meters	In patients not exposed	In patients exposed under 2,500 meters	In patients exposed from 2,501 to 10,000 meters & all nonexposed patients
Necropsy cases, Hiroshima ABCC	153	138	137	154
Surgical pathology cases, Hiroshima ABCC	519	1,576	274	1,821
Total malignant neoplasms	672	1,714	411	1,975
Total patients represented	3,631	8,322	2,074	9,879
Percentage of malignant neoplasms	18.5%	20.6%	19.8%	20.0%

this study they should be considered nonexposed, the calculations were again made, defining the exposed group as only those patients who were within 2,500 meters of the hypocenter. The remainder of the exposed group was added to the controls. Once again, almost no difference of incidence was found in the two groups, either for carcinoma of the stomach or for the incidence of all neoplasms (Tables V and VI).

The total exposed populations were estimated in 1954 to be 47,600 in the 0 to 2,500 meter distance and 50,500 in the 2,501 to 10,000



meter distance. These estimates were based on the Atomic Bomb Casualty Commission's 1949 Radiation Census and on the Japanese National Census of 1950. The incidence of carcinoma of the stomach and of all malignant neoplasms in both of these groups, as shown by material collected at the Hiroshima ABCC pathology department, is demonstrated in Table VII. The small differences in percentages seen here

TABLE VII  
*Carcinoma of the Stomach and All Malignant Neoplasms  
Incidence in Two Exposed Populations*

Distance from the hypocenter	Population	Cases observed at Hiroshima ABCC			
		Carcinoma of the stomach		All malignant neoplasms	
		No. of patients	Incidence	No. of patients	Incidence
0-2,500 meters	47,600	101	.21%	411	.86%
2,501-10,000 meters	50,500	86	.17%	261	.51%

are not considered significant. The incidence for the nonexposed group could not be calculated since this population is a fluid one. Moreover, in the necropsy service, special emphasis has always been placed on obtaining material from exposed cases.

The age distribution of the patients with carcinoma of the stomach was determined (Table VIII), and the exposed group was again di-

TABLE VIII  
*Necropsy and Surgical Records: Carcinoma of the Stomach*

Age	Patients exposed to atomic bomb		Patients not exposed to atomic bomb
	Exposed at 2,500 meters or less	Exposed between 2,500 and 10,000 meters	
21 - 25	0	1	3
26 - 30	2	0	11 (3.2%)
31 - 35	2	2	14 (4.0%)
36 - 40	4	7 (8.1%)	30 (8.6%)
41 - 45	7 (6.9%)	7 (8.1%)	40 (11.5%)
46 - 50	12 (11.9%)	10 (11.6%)	52 (14.9%)
51 - 55	11 (10.9%)	14 (16.3%)	52 (14.9%)
56 - 60	14 (13.9%)	11 (12.8%)	58 (16.7%)
61 - 65	17 (16.8%)	12 (14.0%)	53 (15.2%)
66 - 70	14 (13.9%)	10 (11.6%)	24 (6.9%)
71 - 75	12 (11.9%)	8 (9.3%)	7 (2.0%)
76 - 80	5	3	3
81 - 85	1	1	1
Total	101	86	348

vided into two subgroups: those exposed at 2,500 meters or less and those exposed between 2,500 meters and 10,000 meters. Again there was no significant variation in the incidence among the 3 groups in any 5 year period.

A preliminary analysis of the surgical pathology records indicated that carcinoma of the stomach occurred about 8 times more frequently among men than among women, whether or not exposed. The necropsy material was then examined and showed no significant difference in incidence between males and females. The discrepancy in the surgical pathology records is readily explained in view of the fact that the number of specimens from females is made very much larger by the submission of numerous cervical and breast biopsy specimens. In Japan, even more so than in the United States, these are not equated in the male series. The almost complete absence of prostatic hypertrophy or prostatic carcinoma in Japan<sup>20,21</sup> heightens the difference in numbers of surgical pathology specimens received from men and women.

The data gathered in this study were submitted to the Biostatistics Department in the hope that a real incidence of carcinoma of the stomach per 10,000 people could be calculated for the exposed and nonexposed groups. During the past 18 months, in an effort to give statistical significance to the work carried out at ABCC, the establishment of fixed population samples in Hiroshima for those exposed to the bomb detonation at close distances, those at greater distances, and those not exposed has been under way. The population sample for the nonexposed group is still incomplete, and therefore, it was not possible to calculate a real incidence of carcinoma of the stomach for this group. However, it was found that 42 carcinomas of the stomach from the group exposed under 2,500 meters, and 30 from the group exposed between 2,500 and 10,000 meters were included in the master sample. The population figures for these two groups are now available for the years 1951 through 1956. For these two groups, a valid incidence of carcinoma of the stomach per 10,000 live population could be calculated. This incidence is 1.80 per 10,000 for the group exposed under 2,500 meters and 1.72 per 10,000 for those exposed 2,500 to 10,000 meters. This, of course, constitutes no significant difference.

#### COMMENT AND SUMMARY

Carcinoma of the stomach was listed in 535 cases in the surgical pathology and necropsy pathology records of the Hiroshima Atomic Bomb Casualty Commission between December 1, 1948, and June 30, 1957. Of these patients, 187 had been exposed to the explosion of the atomic bomb in Hiroshima. The cases in the exposed group were com-

pared with those in the nonexposed group, and no significant differences were found between these two groups for the average age at the time of diagnosis, the age distribution in 5 year age groups, the post-operative survival time, or the histologic pattern and location of the tumor in the stomach. The incidence of all neoplasms in the exposed and nonexposed groups was also calculated and found to be almost equal. The possibility that the definition of "exposure" was too broad and was thus hiding effects in the patients exposed at 2,500 meters or less was considered, and the material was re-examined using 2,500 meters from the hypocenter as the limit of exposure. The patients between 2,500 and 10,000 meters were added to the control group. The incidences of carcinoma of the stomach and of all neoplasms were again calculated and again found to be approximately equal. In the cases treated by a surgical resection of the cancer through 1956, a follow-up was possible in 252 patients; 93 of these were still living, but only 7 had lived more than 5 years after the operation. Only one of these was an exposed patient. No significance was attached to this finding.

Carcinoma of the stomach is the most frequent neoplastic disease for both men and women in Japan. Its incidence and behavior in patients exposed and not exposed to the explosion of the atomic bomb in Hiroshima has been compared. No significant differences were found in these two groups. The study represents an 8½ year survey ending almost 12 years after the atomic bombing of Hiroshima.

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